Board of Patent Appeals and Interferences

Patent and Trademark Office (P.T.O.)
*1 EX PARTE DINESH GALA AND DONALD J. DIBENEDETTO
Appeal No. 2001-0987
Application 09/169,109

NO DATE REFERENCE AVAILABLE FOR THIS DOCUMENT

Thomas D. Hoffman

Schering-Plough Corporation

Patent Department K-6-1 1990

2000 Galloping Hill Road

Kenilworth NJ 07033-0530

Before WINTERS, WILLIAM F. SMITH, and ROBINSON

Administrative Patent Judges

Winters

Administrative Patent Judge

ON BRIEF

DECISION ON APPEAL

This appeal was taken from the examiner's decision rejecting claims 1 through 8, which are all of the claims pending in this application.

THE INVENTION

Applicants' invention relates to a crystalline "polymorph form 2 loratadine" having a specified x-ray powder diffraction pattern; a pharmaceutical composition comprising an anti-allergic effective amount of the polymorph form 2 loratadine and a pharmaceutically acceptable carrier; and a method of treating allergic reactions in a mammal by administering to the mammal an anti-allergic effective amount of polymorph form 2 loratadine. Claim 1, which is illustrative of the subject matter on appeal, reads as follows:

1. Polymorph form 2 loratadine having the following x-ray powder diffraction pattern expressed in terms of "d" spacing and relative intensities("RI").

d spacing (+-0.05)	RI
8.95	Weak
6.37	Weak
5.64	Weak

THE REFERENCES

The prior art references relied on by the examiner are:

Villani	4,282,233	Aug. 4, 1981
Sims et al. (Sims) (PCT Application)	WO 95/01792	Jan.19, 1995

THE REJECTIONS

Claims 1 through 8 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combined disclosures of Villani and Sims. Claims 1 through 8 further stand rejected under the judicially created doctrine of obviousness-type double patenting over claim 7 of Villani in view of Sims.

DELIBERATIONS

Our deliberations in this matter have included evaluation and review of the following materials: (1) the instant specification, including Figures 1 and 2, and all of the claims on appeal; (2) the Appeal Brief (Paper No. 10); (3) the Examiner's Answer (Paper No. 11); and (4) the above - cited prior art references.

On consideration of the record, including the above - listed materials, we reverse the examiner's rejections.

DISCUSSION

The question here is whether the combined disclosures of Villani and Sims support a conclusion of obviousness of claims 1 through 8, which recite the crystalline polymorph form 2 of loratadine having a unique x-ray powder diffraction pattern and infrared spectrum. We answer that question in the negative.

*2 Villani discloses polymorph form 1 of loratadine, but does not disclose or suggest that loratadine may assume distinct, crystalline polymorphic forms having different physical properties. Nor does Villani teach a person having ordinary skill in the art how to make polymorph form 2 of loratadine.

The Sims reference does not cure the deficiencies of Villani. Sims discloses a list of 16 non-sedating antihistamines, including loratadine, useful in combination therapy (Sims, page 8, lines 3 through 6). After listing those antihistamines, Sims refers to "a pharmaceutically acceptable salt, hydrate, or polymorph thereof" (id., lines 6 and 7). That reference to pharmaceutically acceptable salts, hydrates, or polymorphs, however, does not teach a person having ordinary skill in the art that loratadine may assume distinct, crystalline polymorphic forms having different physical properties. Rather, it appears that the above-quoted language constitutes boilerplate; and that Sims refers generally to pharmaceutically acceptable salts, hydrates, or polymorphs of any one of 16 non-sedating antihistamines without specifically suggesting that loratadine is capable of existing in the form of distinct crystalline polymorphs. On this point, we disagree with the examiner's finding that "Sims expressly teaches that loratadine may be in the form of polymorphs" (Examiner's Answer, page 3, lines 10 and 11). Nor does Sims teach a person having ordinary skill in the art how to make polymorph form 2 of loratadine.

On this record, applicants, and applicants alone, disclose that "loratadine can exist in the form of two distinct crystalline polymorphs, each having distinctly different physical properties" (Specification, page 2, first full paragraph). Applicants have discovered specific solvents and experimental conditions, producing a distinctly different polymorph form 2 of loratadine (Specification, page 3, last paragraph). Applicants discovered that crystallization of loratadine (prepared as described in U.S. Patent No. 4,282,233) from toluene, t-butylmethylether, heptane, or mixtures thereof, produce a polymorph form 2 loratadine. Applicants also discovered that using a t-butylmethylether-toluene mixture is preferred (Specification, page 4, second paragraph). This information stems from applicants' specification, but not from the cited prior art. Further, neither Villani nor Sims discloses or renders obvious a method for making polymorph form 2 loratadine. As stated in In re Hoeksema, 399 F.2d 269, 274, 158 USPQ 596, 601 (CCPA 1968),

> [I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds. [footnote omitted]

***3** The examiner relies heavily on this proposition of law set forth in Ex parte Hartop, 139 USPQ 525, 527 (Bd. Pat. App. 1962):

> [M]erely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable.

According to the examiner, polymorph form 2 loratadine is merely another form of an old product (polymorph form 1 loratadine) and both forms possess the same utility. Accordingly, the examiner concludes that applicants' claims, reciting polymorph form 2 loratadine, are unpatentable. We disagree. Here, we invite attention to In re Cofer, 354 F.2d 664, 667, 148 USPQ 268, 271 (CCPA 1966), where the court substantially discredited PTO reliance on the above-quoted proposition of law in Hartop. Like the situation presented in Cofer, the examiner in this case has not adequately established that the prior art (1) suggests the polymorph form 2 of loratadine; or (2) discloses or renders obvious a method for making the polymorph form 2 of loratadine.

Accordingly, the examiner's rejection of claims 1 through 8 under 35 U.S.C. § 103(a) as unpatentable over Villani in view of Sims is reversed. For essentially the same reasons, the rejection of claims 1 through 8 under the judicially created doctrine of obviousness-type double patenting over claim 7 of Villani in view of Sims is also reversed.

The examiner's decision rejecting claims 1 through 8 is reversed.

REVERSED

BOARD OF PATENT APPEALS AND INTERFERENCES

Sherman D. Winters

Administrative Patent Judge

William F. Smith

Administrative Patent Judge

Douglas W. Robinson

Administrative Patent Judge

2002 WL 851814 (Bd.Pat.App & Interf.)

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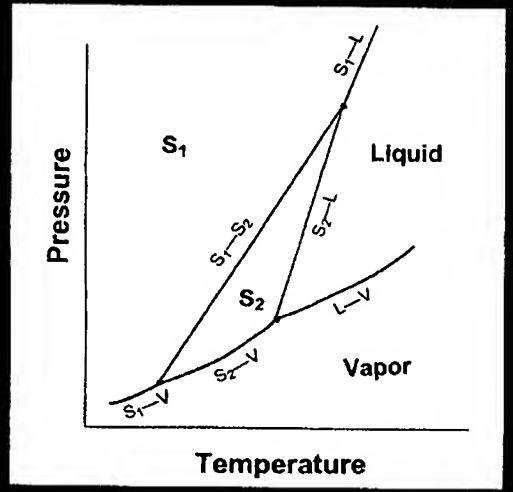
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 95

Polymorphism in Pharmaceutical Solids



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Harry G. Brittain

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Theory and Origin of Polymorphism

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I. INTRODUCTION

Many pharmaceutical solids exhibit *polymorphism*, which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the mol-

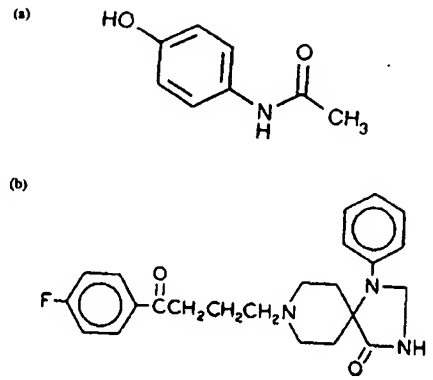


Fig. 1 Molecular structure of (a) acetaminophen and (b) spiperone.

ecules in the crystal lattice [1–3]. Thus, in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules. As a result, the polymorphic solids have different unit cells and hence display different physical properties, including those due to packing, and various thermodynamic, spectroscopic, interfacial, and mechanical properties, as discussed below [1–3].

For example, acetaminophen (paracetamol, 4-acetamidophenol, 4-hydroxyacetanilide, shown in Fig. 1a) can exist as a monoclinic form, of space group $P2_1/n$ [4], which is thermodynamically stable under ambient conditions. The compound can also be obtained as a less stable orthorhombic form, of space group *Pbca*, and which has a higher density indicative of closer packing [5–7]. The unit cells of these two forms are compared in Fig. 2 and Table 1. The molecule of acetaminophen is rigid on account of resonance due to conjugation involving the hy-

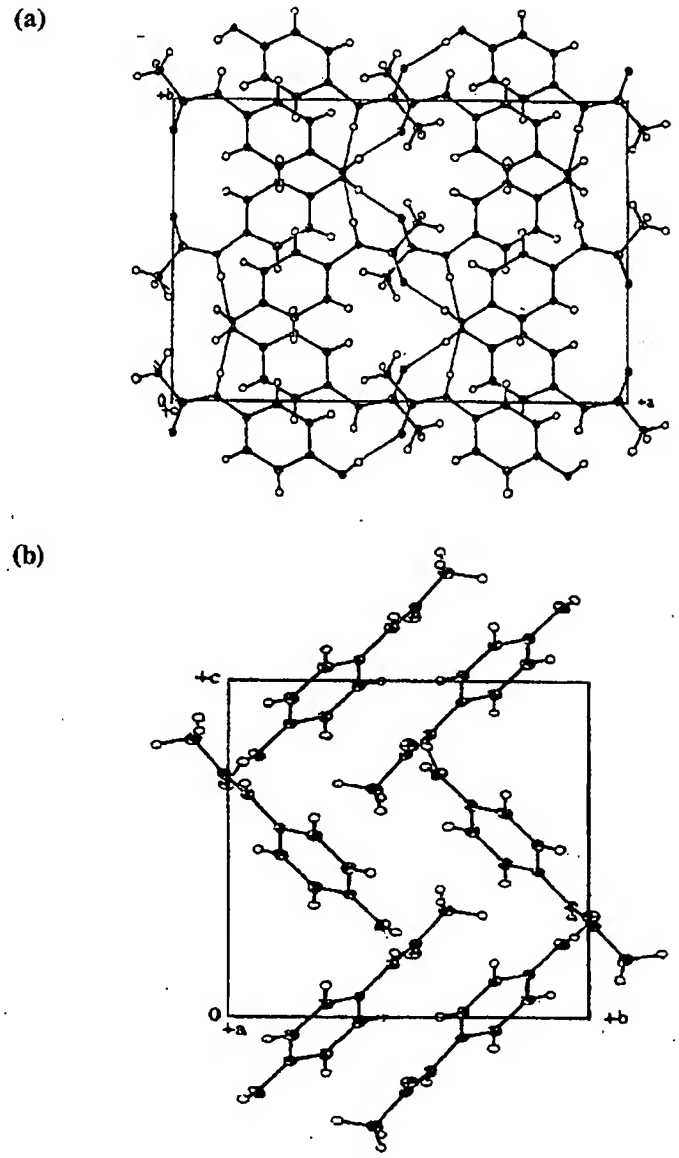


Fig. 2 View of the unit cell contents for two polymorphs of acetaminophen: (a) orthorhombic form (b) monoclinic form [4,5,7]. (Reproduced with permission of the copyright owner, the American Crystallographic Association, Washington, DC.)

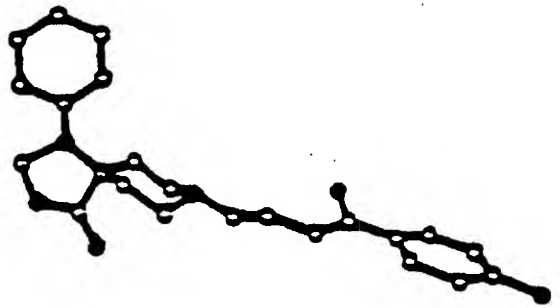
Table 1 Crystal Data for Two Polymorphs of Acetaminophen

Crystal data and structure refinement	Orthorhombic phase	Monoclinic phase
Empirical formula	$C_8H_9NO_2$	$C_8H_9NO_2$
Formula weight	151.16	151.16
Crystal system	Orthorhombic	Monoclinic
Space group	*Pbca*	$P2_1/n$
Unit cell dimensions	a = 17.1657(12) Å	a = 7.0941(12) Å
	b = 11.7773(11) Å	b = 9.2322(11) Å
	c = 7.212(2) Å	c = 11.6196(10) Å
	α = 90.000°	α = 90.000°
	β = 90.000°	β = 97.821(10)°
	γ = 90.000°	γ = 90.000°
Volume	1458.1(4) Å^3	753.9(2) Å^3
Z	8	4
Density (calculated)	1.377 g/cm^3	1.332 g/cm^3
Crystal size	0.28 × 0.25 × 0.15 mm	0.30 × 0.30 × 0.15 mm
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Hydrogen bond lengths and angles		
H(5)O(2)	1.852(26) Å	1.772(20) Å
H(6)O(1)	2.072(28) Å	2.007(18) Å
O(1)—H(5)O(2)	170.80(2.35)°	166.15(1.75)°
N(1)—H(6)O(1)	163.52(2.19)°	163.93(1.51)°

Source: Refs. 4, 5, and 7. Reproduced with permission of the copyright owner, the American Crystallographic Association, Washington, DC.

droxyl group, the benzene ring, and the amido group. Therefore the conformation of the molecule is virtually identical in the two polymorphs of acetaminophen. On the other hand, the spiperone molecule (8-[3-(p-fluorobenzoyl)-propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, shown in Fig. 1b) contains a flexible -CH_2-CH_2-CH_2- chain and is therefore capable of existing in different molecular conformations [8]. Two such conformations, shown in Fig. 3, give rise to two different conformational polymorphs (denoted Forms I and II), which have different unit cells (one of which is shown in Fig. 4) and densities, even

Form I



Form II

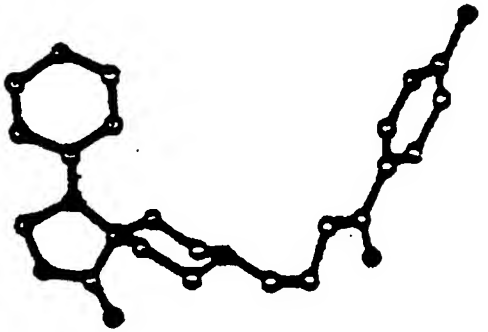


Fig. 3 The molecular conformations of the spiperone molecule in polymorphic forms I and II [8]. (Reproduced with permission of the copyright owner, the American Pharmaceutical Association, Washington, DC.)

though their space groups are the same, both being $P2_1/n$, monoclinic, as shown in Table 2 [8].

As mentioned above, the various polymorphs of a substance can exhibit a variety of different physical properties. Table 3 lists some of the many properties that differ among different polymorphs [1–3,9]. Because of differences in the dimensions, shape, symmetry, capacity

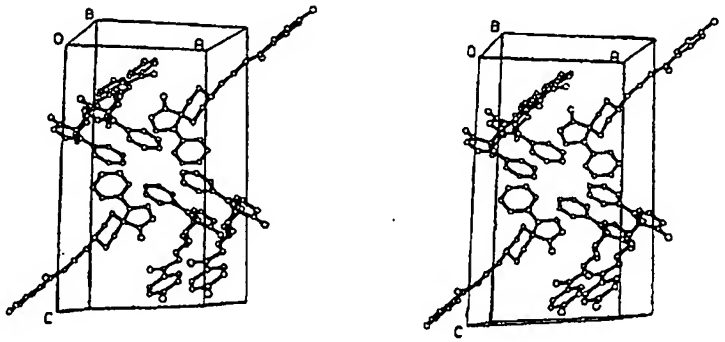


Fig. 4 View of the unit cell contents for the form I polymorph of spiperone [8]. (Reproduced with permission of the copyright owner, the American Pharmaceutical Association, Washington, DC.)

Table 2 Crystal Data for Two Polymorphs of Spiperone

	Form I	Form II
Empirical formula	$C_{23}H_{26}FN_3O_2$	$C_{23}H_{26}FN_3O_2$
Molecular weight	395.46	395.46
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/a$	$P2_1/c$
Unit cell dimensions	$a = 12.722$ Å	$a = 18.571$ Å
	$b = 7.510$ Å	$b = 6.072$ Å
	$c = 21.910$ Å	$c = 20.681$ Å
	$\alpha = 90.00°$	$\alpha = 90.00°$
	$\beta = 95.08°$	$\beta = 118.69°$
	$\gamma = 90.00°$	$\gamma = 90.00°$
Unit cell volume	2085.1 Å^3	2045.7 Å^3
Z	4	4

Source: Ref. 8. Reproduced with permission of the copyright owner, the American Pharmaceutical Association, Washington, DC.

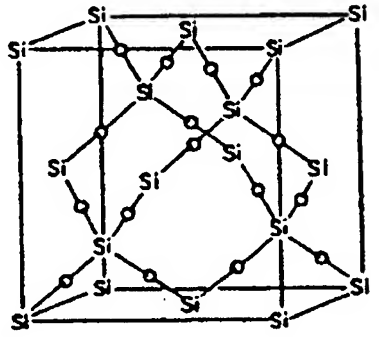
Table 3 List of Physical Properties that Differ Among Various Polymorphs

1. Packing properties
   a. Molar volume and density
   b. Refractive index
   c. Conductivity, electrical and thermal
   d. Hygroscopicity
2. Thermodynamic properties
   a. Melting and sublimation temperatures
   b. Internal energy (i.e., Structural energy)
   c. Enthalpy (i.e., Heat content)
   d. Heat capacity
   e. Entropy
   f. Free energy and chemical potential
   g. Thermodynamic activity
   h. Vapor pressure
   i. Solubility
3. Spectroscopic properties
   a. Electronic transitions (i.e., ultraviolet–visible absorption spectra)
   b. Vibrational transitions (i.e., infrared absorption spectra and Raman spectra)
   c. Rotational transitions (i.e., far infrared or microwave absorption spectra)
   d. Nuclear spin transitions (i.e., nuclear magnetic resonance spectra)
4. Kinetic properties
   a. Dissolution rate
   b. Rates of solid state reactions
   c. Stability
5. Surface properties
   a. Surface free energy
   b. Interfacial tensions
   c. Habit (i.e., shape)
6. Mechanical properties
   a. Hardness
   b. Tensile strength
   c. Compactibility, tableting
   d. Handling, flow, and blending

(number of molecules), and void volumes of their unit cells, the different polymorphs of a given substance have different physical properties arising from differences in molecular packing. Such properties include molecular volume, molar volume (which equals the molecular volume multiplied by Avogadro's number), density (which equals the molar mass divided by the molar volume), refractive index in a given direction (as a result of the interactions of light quanta with the vibrations of the electrons in that direction), thermal conductivity (as a result of the interaction of infrared quanta with the intramolecular and intermolecular vibrations and rotations of the molecules), electrical conductivity (as a result of movement of the electrons in an electric field), and hygroscopicity (as a result of access of water molecules into the crystal and their interactions with the molecules of the substance). Differences in melting point of the various polymorphs arise from differences of the cooperative interactions of the molecules in the solid state as compared with the liquid state. Differences in the other thermodynamic properties among the various polymorphs of a given substance are discussed below. Also involved are differences in spectroscopic properties, kinetic properties, and some surface properties. Differences in packing properties and in the energetics of the intermolecular interactions (thermodynamic properties) among polymorphs give rise to differences in mechanical properties.

Many pharmaceutical solids can exist in an amorphous form, which, because of its distinctive properties, is sometimes regarded as a polymorph. However, unlike true polymorphs, amorphous forms are not crystalline [1,2,10]. In fact, amorphous solids consist of disordered arrangements of molecules and therefore possess no distinguishable crystal lattice nor unit cell and consequently have zero crystallinity. In amorphous forms, the molecules display no long-range order, although the short-range intermolecular forces give rise to the short-range order typical of that between nearest neighbors (see Fig. 5). Thermodynamically, the absence of stabilizing lattice energy causes the molar internal energy or molar enthalpy of the amorphous form to exceed that of the crystalline state. The absence of long-range order causes the molar entropy of the amorphous form to exceed that of the crystalline state. Furthermore, the lower stability and greater reactivity of the amorphous form indicates that its molar Gibbs free energy exceeds that of the crys-

(a)



(b)

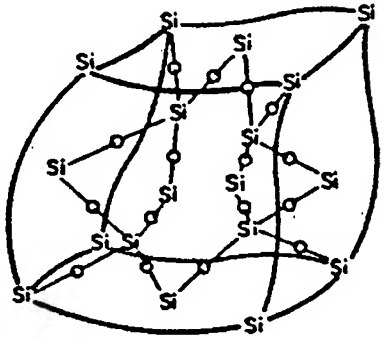


Fig. 5 Schematic diagram showing the difference in long-range order of silicon dioxide in (a) the crystalline state (crystobalite) and (b) the amorphous state (silica glass) [2]. The two forms have the same short-range order. (Reproduced with permission of the copyright owner, the American Pharmaceutical Association, Washington, DC.)

talline state. This observation implies that the increased molar enthalpy of the amorphous form outweighs the $T\Delta S$ term that arises from its increased molar entropy.

II. THERMODYNAMICS OF POLYMORPHS

The energy of interaction between a pair of molecules in a solid, liquid, or real gas depends on the mean intermolecular distance of separation according to the Morse potential energy curve shown in Fig. 6 [11,12]. For a given pair of molecules, each polymorph, liquid or real gas has its own characteristic interaction energies and Morse curve. These intermolecular Morse curves are similar in shape but have smaller energies and greater distances than the Morse potential energy curve for the interaction between two atoms linked by a covalent bond in a diatomic molecule or within a functional group of a polyatomic molecule. The Morse potential energy curve in Fig. 6 is itself the algebraic sum of a curve for intermolecular attraction due to van der Waals forces or hydrogen bonding and a curve for intermolecular electron–electron and nucleus–nucleus repulsion at closer approach. The convention employed is that attraction causes a decrease in potential energy, whereas repulsion causes an increase in potential energy. At the absolute zero of temperature, the pair of molecules would occupy the lowest or zero point energy level. The Heisenberg uncertainty principle requires that the molecules have an indeterminate position at a defined momentum or energy. This indeterminate position corresponds to the familiar vibration of the molecules about the mean positions that define the mean intermolecular distance. At a temperature T above the absolute zero, a proportion of the molecules will occupy higher energy levels according to the Boltzmann equation:

$$\frac{N_1}{N_0} = \exp\left(\frac{-\Delta\varepsilon_1}{kT}\right) \tag{1}$$

where N_1 is the number of molecules occupying energy level 1 (for which the potential energy exceeds the zero point level by the energy difference $\Delta\varepsilon_1$), N_0 is the number of molecules occupying the zero point

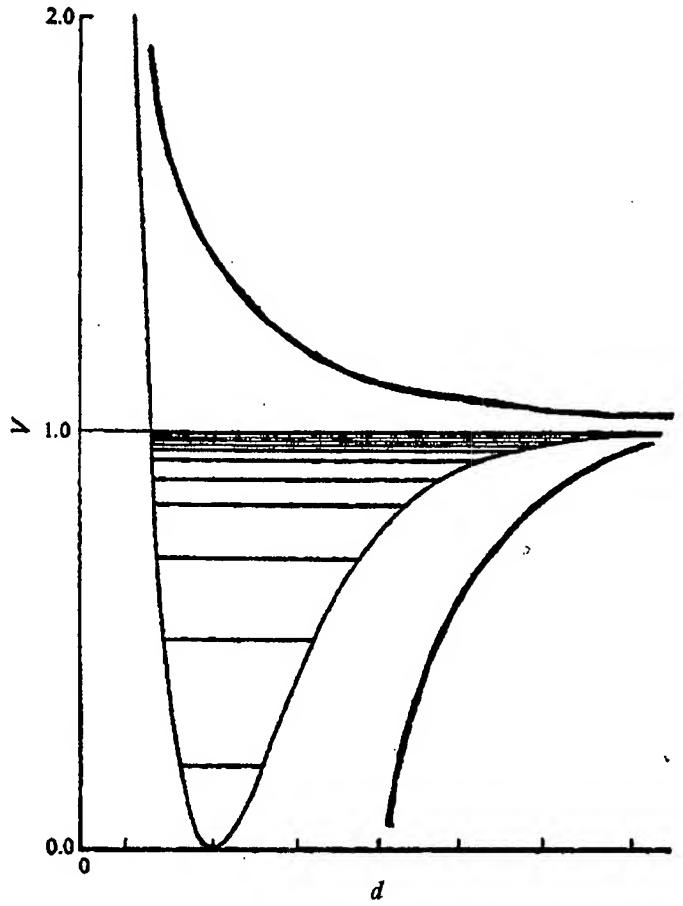


Fig. 6 Morse potential energy curve of a given condensed phase, solid or liquid [11]. The potential energy of interaction V is plotted against the mean intermolecular distance d. (Reproduced with permission of the copyright owner, Oxford University Press, Oxford, UK.)

level, and k is the Boltzmann constant (1.381×10^{-23} J/K, or 3.300×10^{-26} cal/K, i.e. the gas constant per molecule).

With increasing temperature, increasing numbers of molecules occupy the higher energy levels so that the distribution of the molecules among the various energy levels (known as the Boltzmann distribution) becomes broader, as shown in Fig. 7. At any given temperature, the number of distinguishable arrangements of the molecules of the system among the various energy levels (and positions in space) available to them is termed the thermodynamic probability Ω. With increasing temperature, Ω increases astronomically. According to the Boltzmann equation,

$$S = k \cdot \ln \Omega \tag{2}$$

where the entropy S is a logarithmic function of Ω, so increasing temperature causes a steady rise, though not an astronomical rise, in the entropy. In a macroscopic system, such as a given polymorph, the product $T \cdot S$ represents the energy of the system that is associated with

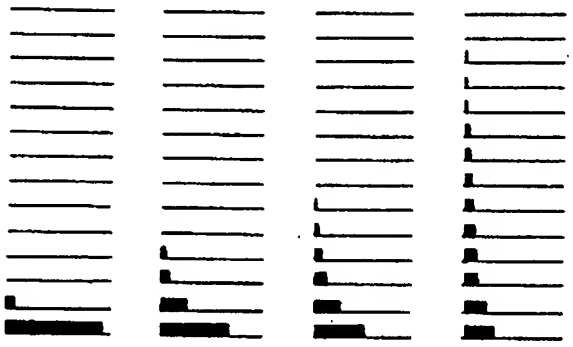


Fig. 7 Populations of molecular states at various temperatures [11]. The temperature is increasing from left to right. (Reproduced with permission of the copyright owner, Oxford University Press, Oxford, UK.)

the disorder of the molecules. This energy is the bound energy of the system that is unavailable for doing work.

The sum of the individual energies of interaction between nearest neighbors, next nearest neighbors, and so on, throughout the entire crystal lattice, liquid, or real gas can be used to define the internal energy E (i.e., the intermolecular structural energy) of the phase. Normally the interactions beyond next nearest neighbors are weak enough to be approximated or even ignored. For quantitative convenience one mole of substance is considered, corresponding to molar thermodynamic quantities. At constant pressure P (usually equal to atmospheric pressure), the total energy of a phase is represented by the enthalpy H:

$$H = E + P \cdot V \tag{3}$$

where V is the volume of the phase (the other quantities have already been defined). With increasing temperature, E, V, and H tend to increase.

Figure 8 shows that the enthalpy H and the entropy S of a phase

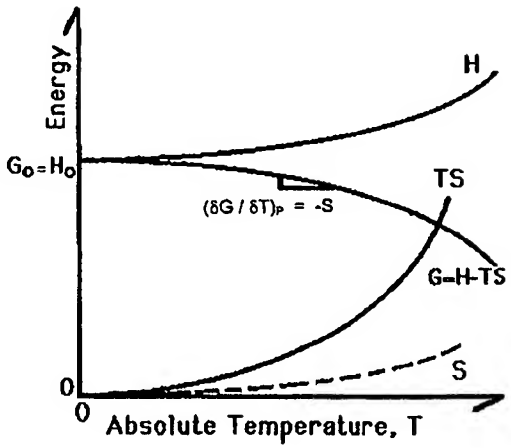


Fig. 8 Plots of various thermodynamic quantities against the absolute temperature T of a given solid phase (polymorph) or liquid phase at constant pressure. H = enthalpy, S = entropy, and G = Gibbs free energy.

tend to increase with increasing absolute temperature T. According to the third law of thermodynamics, the entropy of a perfect, pure crystalline solid is zero at the absolute zero of temperature. The product $T \cdot S$ increases more rapidly with increasing temperature than does H. Hence the Gibbs free energy G, which is defined by

$$G = H - T \cdot S \tag{4}$$

tends to decrease with increasing temperature (Fig. 8). This decrease also corresponds to the fact that the slope ($\delta G/\delta T$) of the plot of G against T is negative according to the equation

$$\left(\frac{\delta G}{\delta T}\right)_p = -S \tag{5}$$

As already stated, the entropy of a perfect, pure crystalline solid is zero at the absolute zero of temperature. Hence the value of G at $T = 0$ (termed G_0) is equal to the value of H at $T = 0$, termed H_0 (Fig. 8). Each polymorph yields an energy diagram similar to that of Fig. 6, although the values of G, H, and the slopes of the curves at a given temperature are expected to differ between different polymorphs.

Because each polymorph has its own distinctive crystal lattice, it has its own distinctive Morse potential energy curve for the dependence of the intermolecular interaction energies with intermolecular distance. The liquid state has a Morse curve with greater intermolecular energies and distances, because the liquid state has a higher energy and molar volume (lower density) than does the solid state. Figure 9 presents a series of Morse curves, one for each polymorph (A, B, and C) and for the liquid state of a typical substance of pharmaceutical interest. The composite curve in Fig. 9 is the algebraic sum of the Morse curves for each phase (polymorph or liquid). The dashed line corresponds to the potential energy of the separated, noninteracting molecules in the gaseous state. The increase in potential energy from the zero point value of a given polymorph to the dashed line corresponds to the lattice energy of that polymorph or energy of sublimation (if at constant pressure, the enthalpy of vaporization). For the liquid state the increase in potential energy from the average value in the liquid state to the dashed line for the gaseous molecules corresponds to the energy of vaporization (if at constant pressure, the enthalpy of vaporization). The increase in potential energy from the zero point value of a given polymorph to the average value for the liquid state corresponds to the energy of fusion (if at constant pressure, the enthalpy of fusion).

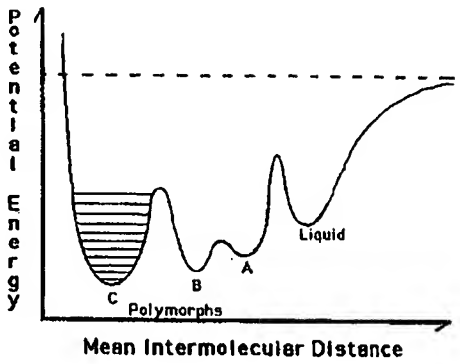


Fig. 9 Composite Morse potential energy curve of a series of polymorphs, A, B, and C, and of the corresponding liquid phase.

When comparing the thermodynamic properties of polymorph 1 and polymorph 2 (or of one polymorph 1 and the liquid state 2) the difference notation is used:

$$\Delta G = G_2 - G_1 \tag{6}$$

$$\Delta S = S_2 - S_1 \tag{7}$$

$$\Delta H = H_2 - H_1 \tag{8}$$

$$\Delta V = V_2 - V_1 \tag{9}$$

In discussions of the relative stability of polymorphs and the driving force for polymorphic transformation at constant temperature and pressure (usually ambient conditions), the difference in Gibbs free energy is the decisive factor and is given by

$$\Delta G = \Delta H - T\,\Delta S \tag{10}$$

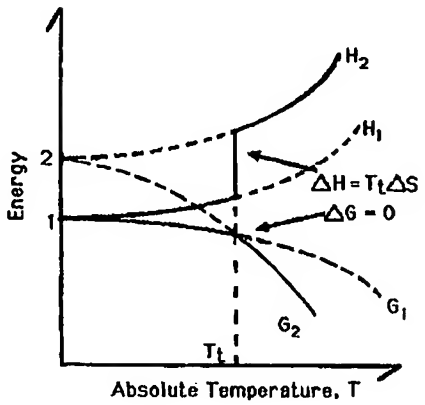


Fig. 10 Plots of the Gibbs free energy G and the enthalpy H at constant pressure against the absolute temperature T for a system consisting of two polymorphs, 1 and 2 (or a solid, 1, and a liquid, 2). T_t is the transition temperature (or melting temperature) and S is the entropy.

Figure 10 shows the temperature dependence of G and H for two different polymorphs 1 and 2 (or for a solid 1, corresponding to any polymorph, and a liquid 2) [13]. In Fig. 10 the free energy curves cross. At the point of intersection, known as the transition temperature T_t (or the melting point for a solid and a liquid), the Gibbs free energies of the two phases are equal, meaning that the phases 1 and 2 are in equilibrium (i.e., $\Delta G = 0$). However, at T_t Fig. 10 shows that polymorph 2 (or the liquid) has an enthalpy H_2 that is higher than that of polymorph 1 (or the solid), so that $H_2 > H_1$. Equations 10 and 6 show that, if $\Delta G = 0$, polymorph 2 (or the liquid) also has a higher entropy S_2 than does polymorph 1 (or the solid), so that $S_2 > S_1$. Therefore according to Equation 10, at T_t,

$$\Delta H_t = T_t \Delta S_t \tag{11}$$

where $\Delta H_t = H_2 - H_1$ and $\Delta S_t = S_2 - S_1$ at T_t. By means of differential scanning calorimetry, the enthalpy transition ΔH_t (or the enthalpy of fusion ΔH_f) may be determined. For a polymorphic transition, the rate

of temperature increase must be slow enough to allow polymorph 1 to change completely to polymorph 2 over a few degrees. Because in Fig. 10, $H_2 > H_1$, ΔH is positive and the transition is endothermic in nature.

Figure 10 shows that, below T_t, polymorph 1 (or the solid) has the lower Gibbs free energy and is therefore more stable (i.e., $G_2 > G_1$). On the other hand, above T_t, polymorph 2 (or the liquid) has the lower Gibbs free energy and is therefore more stable (i.e., $G_2 < G_1$). Under defined conditions of temperature and pressure, only one polymorph can be stable, and the other polymorph(s) are unstable. If a phase is unstable but transforms at an imperceptibly low rate, then it is sometimes said to be metastable.

The Gibbs free energy difference ΔG between two phases reflects the ratio of "escaping tendencies" of the two phases. The escaping tendency is termed the fugacity f and is approximated by the saturated vapor pressure, p. Therefore

$$\Delta G = RT \ln\left(\frac{f_2}{f_1}\right) \tag{12}$$

$$\sim RT \ln\left(\frac{p_2}{p_1}\right) \tag{13}$$

where the subscripts 1 and 2 refer to the respective phases, R is the universal gas constant, and T is the absolute temperature. The fugacity is proportional to the thermodynamic activity a (where the constant of proportionality is defined by the standard state), while thermodynamic activity is approximately proportional to the solubility s (in any given solvent) provided the laws of dilute solution apply. Therefore

$$\Delta G = RT \ln\left(\frac{a_2}{a_1}\right) \tag{14}$$

$$\sim RT \ln\left(\frac{s_2}{s_1}\right) \tag{15}$$

in which the symbols have been defined above. Hence, because the most stable polymorph under defined conditions of temperature and pressure has the lowest Gibbs free energy, it also has the lowest values

of fugacity, vapor pressure, thermodynamic activity, and solubility in any given solvent. During the dissolution process, if transport-controlled under sink conditions and under constant conditions of hydrodynamic flow, the dissolution rate per unit surface area J is proportional to the solubility according to the Noyes–Whitney [14] equation; therefore

$$\Delta G = RT \ln\left(\frac{J_2}{J_1}\right) \tag{16}$$

According to the law of mass action, the rate r of a chemical reaction (including the decomposition rate) is proportional to the thermodynamic activity of the reacting substance. Therefore

$$\Delta G = RT \ln\left(\frac{r_2}{r_1}\right) \tag{17}$$

To summarize, the most stable polymorph has the lowest Gibbs free energy, fugacity, vapor pressure, thermodynamic activity, solubility, and dissolution rate per unit surface area in any solvent, and rate of reaction, including decomposition rate.

II. ENANTIOTROPY AND MONOTROPY

If as shown in Fig. 10 one polymorph is stable (i.e., has the lower free energy content and solubility over a certain temperature range and pressure), while another polymorph is stable (has a lower free energy and solubility over a different temperature range and pressure), the two polymorphs are said to be enantiotropes, and the system of the two solid phases is said to be enantiotropic. For an enantiotropic system a reversible transition can be observed at a definite transition temperature, at which the free energy curves cross before the melting point is reached. Examples showing such behavior include acetazolamide, carbamazepine, metochlopramide, and tolbutamide [9,14,15].

Sometimes only one polymorph is stable at all temperatures below the melting point, with all other polymorphs being therefore unstable. These polymorphs are said to be monotropes, and the system of the two solid phases is said to be monotropic. For a monotropic system

the free energy curves do not cross, so no reversible transition can be observed below the melting point. The polymorph with the higher free energy curve and solubility at any given temperature is, of course, always the unstable polymorph. Examples of this type of system include chloramphenicol palmitate and metolazone [9,14,15].

To help decide whether two polymorphs are enantiotropes or monotropes, Burger and Ramberger developed four thermodynamic rules [14]. The application of these rules was extended by Yu [15]. The most useful and applicable of the thermodynamic rules of Burger and Ramberger are the heat of transition rule and the heat of fusion rule. Figure 11, which includes the liquid phase as well as the two polymorphs, illustrates the use of these rules. The heat of fusion rule states that, if an endothermic polymorphic transition is observed, the two forms are enantiotropes. Conversely, if an exothermic polymorphic transition is observed, the two forms are monotropes.

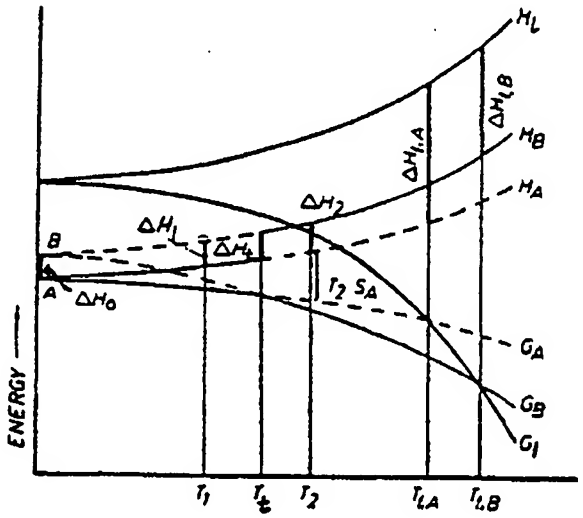
The heat of fusion rule states that, if the higher melting polymorph has the lower heat of fusion, the two forms are enantiotropes. Conversely, if the higher melting polymorph has the higher heat of fusion, the two forms are monotropes. Figure 11, which includes the liquid phase as well as the two polymorphs, is necessary to illustrate the heat of fusion rule.

The above conditions, that are implicit in the thermodynamic rules, are summarized in Table 4. The last two rules in Table 4, the infrared rule and the density rule, were found by Burger and Ramberger [14] to be significantly less reliable than the heat of transition rule and the heat of fusion rule and are therefore not discussed here.

IV. KINETICS OF CRYSTALLIZATION

Among the various methods for preparing different polymorphs are sublimation, crystallization from the melt, crystallization from supercritical fluids, and crystallization from liquid solutions. In the pharmaceutical sciences, different polymorphs are usually prepared by crystallization from solution employing various solvents and various temperature regimes, such as initial supersaturation, rate of de-supersaturation, or final supersaturation. The supersaturation of the solution

(a)



(b)

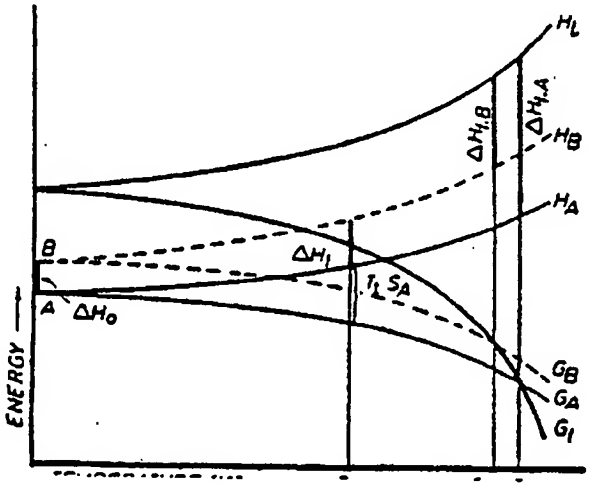


Table 4 Thermodynamic Rules for Polymorphic Transitions According to Burger and Ramberger [14], Where Form I is the Higher-Melting Form

Enantiotropy	Monotropy
Transition < melting I	Transition > melting I
I Stable > transition	I always stable
II Stable < transition	
Transition reversible	Transition irreversible
Solubility I higher < transition	Solubility I always lower than II
Solubility I lower > transition	
Transition II → I is endothermic	Transition II → I is exothermic
$\Delta H_f^{\mathrm{I}} < \Delta H_f^{\mathrm{II}}$	$\Delta H_f^{\mathrm{I}} > \Delta H_f^{\mathrm{II}}$
IR peak I before II	IR peak I after II
Density I < density II	Density I > density II

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that is necessary for crystallization may be achieved by evaporation of the solvent (although any impurities will be concentrated), cooling the solution from a known initial supersaturation (or heating the solution if the heat of solution is exothermic), addition of a poor solvent (sometimes termed a precipitant), chemical reaction between two or more soluble species, or variation of pH to produce a less soluble acid or base from a salt or vice versa (while minimizing other changes in composition).

During the 19th century, Gay Lussac observed that, during crystallization, an unstable form is frequently obtained first that subsequently transforms into a stable form [13]. This observation was later explained thermodynamically by Ostwald [13,16–19], who formulated the law of successive reactions, also known as Ostwald's step rule. This

Fig. 11 Plots of the Gibbs free energy G and the enthalpy H at constant pressure against the absolute temperature T for a system consisting of two polymorphs, A and B, and a liquid phase, l [14]. T_t is the transition temperature, T_f is the melting temperature, and S is the entropy for (a) an enantiotropic system and (b) a monotropic system. (Reproduced with permission of the copyright owner, Springer Verlag, Vienna, Austria.)

rule may be stated as, "In all processes, it is not the most stable state with the lowest amount of free energy that is initially formed, but the least stable state lying nearest in free energy to the original state [13]."

Ostwald's step rule [13,16–19] is illustrated by Fig. 12. Let an enantiotropic system (Fig. 12a) be initially in a state represented by point X, corresponding to an unstable vapor or liquid or to a supersaturated solution. If this system is cooled, the Gibbs free energy will de-

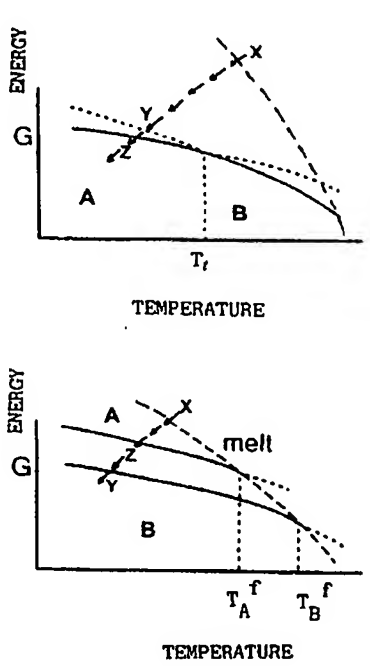

Fig. 12 Relationship between the Gibbs free energy G and the temperature T for two polymorphs for (a) an enantiotropic system and (b) a monotropic system in which the system is cooled from point X [9]. The arrows indicate the direction of change. (Reproduced with permission of the copyright owner, Elsevier, Amsterdam, The Netherlands.)

crease as the temperature decreases. When the state of the system reaches point Y, form B will tend to be formed instead of form A, because according to Ostwald's step rule Y (not Z) is the least stable state lying nearest in free energy to the original state. Similarly, let a monotropic system (Fig. 12b) be initially in a state represented by point X, corresponding to an unstable vapor or liquid or to a supersaturated solution. If this system is cooled, the Gibbs free energy will decrease as the temperature decreases. When the state of the system reaches point Z, form A will tend to be formed instead of form B, because according to Ostwald's step rule Z (not Y) is now the least stable state lying nearest in free energy to the original state. This rule is not an invariable thermodynamic law but a useful practical rule that is based on kinetics, and it is not always obeyed.

An understanding of the kinetics of the crystallization process involves consideration of the various steps involved. In the first step (termed nucleation) tiny crystallites of the smallest size capable of independent existence (termed nuclei) are formed in the supersaturated phase. Molecules of the crystallizing phase then progressively attach themselves to the nuclei, which then grow to form macroscopic crystals in the process known as crystal growth, until the crystallization medium is no longer supersaturated because saturation equilibrium has now been achieved. If the crystals are now allowed to remain in the saturated medium, the smaller crystals, which have a slightly greater solubility according to the Thomson (Kelvin) equation [11,20], tend to dissolve. At the same time, the larger crystals, which consequently have a lower solubility, tend to grow. This process of the growth of larger crystals at the expense of smaller crystals is sometimes termed Ostwald ripening.

The nucleation step is the most critical for the production of different polymorphs and is therefore discussed in some detail below. Nucleation may be primary (which does not require preexisting crystals of the substance that crystallizes) or secondary (in which nucleation is induced by preexisting crystals of the substance). Primary nucleation may be homogeneous, whereby the nuclei of the crystallizing substance arise spontaneously in the medium in which crystallization occurs, or heterogeneous, whereby the nuclei comprise foreign solid matter, such as particulate contaminants (including dust particles or the walls of the container).

Heterogeneous (i.e., spontaneous) nucleation is a stochastic process that is governed by the algebraic opposition of a volume term that favors the accretion of additional molecules from the supersaturated medium and a surface term that favors the dissolution of the molecular aggregates that would otherwise form nuclei. The resulting curve (Fig. 13) resembles an inverted Morse curve [21]. The molecules of the crystallizing substance tend to aggregate in the supersaturated medium under the influence of the volume term that tends to reduce the Gibbs free energy of the system. The prenuclear aggregates, termed embryos, are relatively small and have a high ratio of surface area to volume. The smaller the embryos, the larger will be the surface-to-volume ratio, and the more effective is the surface term in causing the embryos to

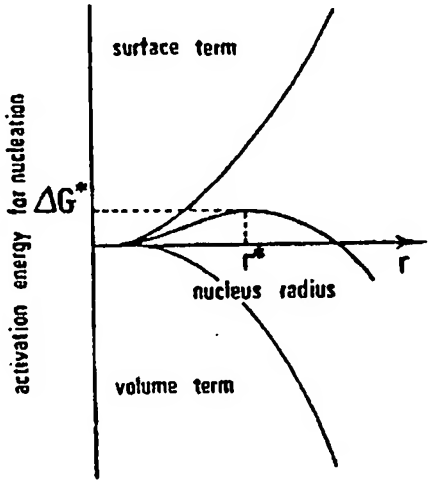

Fig. 13 Plot of the Gibbs free energy G of molecular aggregates (embryos) that are capable of forming nuclei against the size (mean radius r) of the aggregates [21]. ΔG^* is the activation energy for the formation of a nucleus of critical size r^* at which the nucleus can spontaneously grow (G decreases as r increases) or dissolve (G decreases as r decreases) by addition or removal of a single molecule. (Reproduced with permission of the copyright owner, Academic Press, New York, NY.)

dissolve. The resultant free energy curve in Fig. 13 has a maximum corresponding to the critical nuclear aggregate of critical radius r^* and representing an activation energy barrier ΔG^*. Embryos of smaller radius than r^* tend to dissolve, whereas those larger than r^* are true nuclei that tend to grow to form macroscopic crystals [21].

V. NUCLEATION OF POLYMORPHS

For a substance capable of existing in two or more polymorphic forms, each polymorph has its own characteristic curve typified by Fig. 13, each with its own characteristic value of r^* and ΔG^*. Within the limits imposed by their characteristic curves, the aggregates or embryos of the various polymorphs compete for molecules as depicted in Fig. 14 [22]. Depending on the nature of its curve, the aggregate present at the highest concentration (or for which the critical activation energy is the lowest) will form the first nucleus leading to the crystallization of that particular polymorph [22]. This mechanism explains the usual situation in which one polymorph crystallizes depending on the conditions that exist. However, examples are known in which more than one polymorph is obtained in the crystallization process. In these cases, conditions presumably exist whereby more than one type of nucleus is formed in the supersaturated medium at about the same time.

The formation of prenuclear molecular aggregates or embryos in a supersaturated solution can be studied by various physical methods, such as laser Raman spectroscopy [23], a technique that is especially

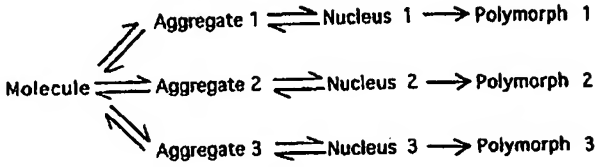

Fig. 14 Nucleation of polymorphs. The aggregate present at the highest concentration, or for which the critical activation energy is lowest, will form the first nucleus leading to the crystallization of that particular polymorph. (Reproduced with permission from Ref. 22.)

useful for aqueous solutions. The vibrational spectra of the aggregates contain peaks that are characteristic of some of the intermolecular interactions (such as hydrogen bonding) that are present in the solid phase that ultimately crystallizes. By appropriate examination of the supersaturated solution, perhaps by spectroscopic methods such as laser Raman spectroscopy [23], it may be possible to identify the intermolecular interaction in the aggregates and hence to identify the nature of the polymorph that will form before it actually crystallizes.

The foregoing theoretical discussion on nucleation, and on the factors that influence nucleation, readily explains why and how the following factors determine the polymorph that crystallizes out: solvent medium, supersaturation, temperature, impurities or additives dissolved, surface of the crystallization vessel, suspended particles, and seed crystals.

Under appropriate thermodynamic conditions discussed at the beginning of this chapter, a less stable polymorph may be converted into a more stable polymorph. The rate of conversion to the more stable polymorph is often rapid, if mediated by the solution phase or vapor phase. In these phases the less stable polymorph (having the greater solubility or vapor pressure) dissolves or sublimes, while the more stable polymorph (having the lower solubility or vapor pressure) crystallizes out. The rate of conversion to the more stable polymorph is usually slower, if the transformation proceeds directly from one solid phase to another. In this case, the mechanism of interconversion is likely to involve the following three steps: (1) loosening and breaking of the intermolecular forces (not covalent bonds) in the less stable polymorph, (2) formation of a disordered solid, similar to a localized amorphous form, and (3) formation of new intermolecular forces leading to crystallization of the more stable polymorph as the product phase [24].

We have seen earlier in this chapter that for an enantiotropic system, one polymorph may transform to another polymorph on the appropriate side of the transition temperature. Figure 15 [9] shows a plot of the rate of polymorphic change as a function of temperature. Close to the transition temperature, the rate is minimal but increases at higher temperatures, at which I → II, or at lower temperatures, at which II → I. If the temperature is lower than a certain optimal value, the rate of polymorphic change of II → I decreases based on the rules of chemical

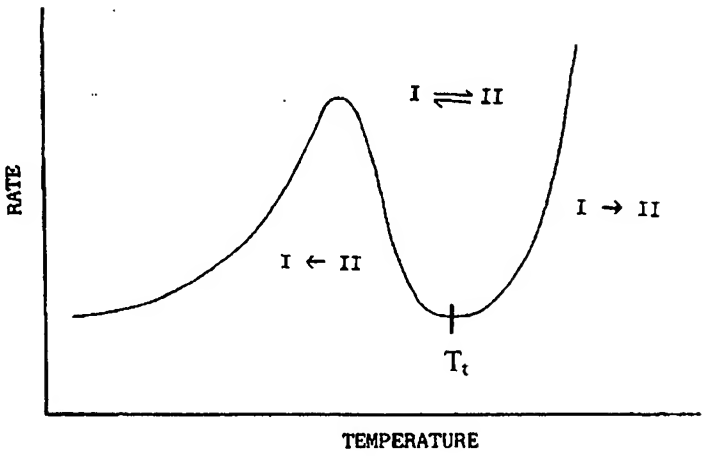

Fig. 15 Temperature dependence of the rates of transformation for a typical first-order transition between a low-temperature polymorph (I) and a high temperature polymorph (II) in an enantiotropic system for which T_t is the transition temperature [9]. (Reproduced with permission of the copyright owner, Elsevier, Amsterdam, The Netherlands.)

kinetics. At temperatures much lower than the transition temperature, the rate of change II → I may be negligible, explaining the observation that the higher temperature polymorph II is metastable at sufficiently low temperatures [9].

VI. NEW OR DISAPPEARING POLYMORPHS

We have seen that the nature of the polymorph that crystallizes depends on the relative rates of nucleation of the polymorphs. These kinetic factors also explain why solid state transformations in molecular crystals often display pronounced hysteresis [25]. For example, to induce the transition of the low-temperature enantiotrope to the high-temperature form, the former may have to be heated well above the transition temperature. Analogously, the absence of a solid state transformation

of the lower melting form below the melting point may not necessarily indicate monotropy but could merely arise from slow nucleation of an enantiotropic transition. Similarly, on cooling the high-temperature form, transformations to the low-temperature form are usually associated with hysteresis. Thus X-ray diffraction studies of crystals have been achieved at 100K, well below (by more than 200K) the temperature range of thermodynamic stability. For example, single-crystal X-ray structural analysis was performed at 98K on the white high-temperature polymorph of dimethyl-3,6-dichloro-2,5-dihydroxyterephthalate, although this polymorph is thermodynamically unstable below 340K [26,27]. Thus a metastable high-temperature form can sometimes remain kinetically stable well below the transition point.

There are several documented examples of the inability to obtain a previously prepared crystal form [27,28]. Dunitz and Bernstein [25] quoted the following passage by Webb and Anderson [29], "Within the fraternity of crystallographers anecdotes abound about crystalline compounds which, like legendary beasts, are observed once and then never seen again." Similar anecdotes have been recounted by some industrial pharmaceutical scientists prior to 1970, but published reports relating to drugs and excipients are exceedingly difficult to find, undoubtedly because they would indicate a lack of process control. Most crystallographers and preformulation scientists recognize the role of seeding in initiating nucleation, and many consider the disappearance of a metastable form to be a local and temporary phenomenon. Jacewicz and Nayler [30] concluded that "any authentic crystal form should be capable of being re-prepared, although selection of the right conditions may require some time and trouble."

The chemical and pharmaceutical literature documents a number of examples of crystal forms that were apparently displaced by a more stable polymorph. One example is benzocaine picrate, for which a crystal form melting at 129–132°C was referred to in the 1968 edition of the *Pharmacopoeia Nordica* as one of the identification tests for the local anesthetic. The 8th edition of the *Merck Index* (1968) gives 134°C as the melting point [31]. Nielsen and Borka [32] described a more stable polymorph melting at 162–163°C, which can be obtained by drying the original lower-melting form at 105°C for two or more hours or by vacuum drying at 100°C and 0.1 mmHg with or without sublimation. On a hot stage under a microscope, the phase-pure polymorphs melt at 132–133°C or 162–163°C, respectively. A partially transformed sample that contains both polymorphs partially melts at 132°C, whereupon the molten benzocaine picrate resolidifies within seconds [32]. The new resolidified crystals that grow from the liquid phase are found to melt at 162–163°C, typical of the more stable polymorph. The infrared spectra of the two polymorphs differ mainly around 3500 cm^{-1} and in the 1500–1700 cm^{-1} region [32]. The authors report [32] that, once the stable (higher-melting) form had been obtained in either of the two laboratories, the metastable (lower-melting) polymorph could no longer be isolated. Most significantly, it was reported that the lower-melting polymorph could be isolated again after discarding all the samples, washing the equipment and laboratory benches, and waiting for 8–12 days. This cleansing procedure had been repeated several times in the laboratories of the above authors, who commented "Obviously, the seeding effect during the formation of the primary crystals (or during the very procedure of determination of the melting point) is exceptionally strong" [32]. After these findings the monograph in the 1973 edition of the *Pharmacopoeia Nordica* was modified, stating that benzocaine picrate has a melting point between 161°C and 164°C and may be formed as a metastable modification with melting point between 129°C and 132°C, which will not in every case be transformed into the higher-melting modification during the determination of the melting point [32].

Another example of the displacement of a metastable polymorph by a stable polymorph is xylitol (the RS or meso form), which is used as a sweetening agent in tablets, syrups, and coatings and as an alternative to sucrose in foods, confectionery, and toiletries [33–35]. Xylitol is also described in a NF monograph [36]. In the early 1940s, two polymorphs of xylitol were described. One of these is a metastable, hygroscopic, monoclinic form, melting at 61–61.5°C [37] and the other a stable orthorhombic form melting at 93–94.5°C [38]. After a sample of the orthorhombic form was introduced into a laboratory in which the monoclinic polymorph had been prepared, the latter "changed in a few days into the high-melting and stable form on exposure to the air of the laboratory" [38]. Later, Kim and Jeffrey determined the crystal structure of the stable orthorhombic polymorph [39]. These authors

stated, "Attempts to obtain the lower melting monoclinic form from alcoholic solutions either at room temperature or close to 0°C have hitherto been unsuccessful. We invariably grow the orthorhombic crystals. It is interesting to note that although xylitol was first prepared as a syrup in 1891 there was no report of crystallization until fifty years later, when it was the metastable hygroscopic form that was prepared first. Having now obtained the stable form, it is difficult to recover the metastable crystals . . . The availability of appropriate nuclei in the laboratory is clearly a determining factor, as is well known to carbohydrate chemists [39]."

Since the late 1980s, solid state chemists and pharmaceutical scientists have increasingly recognized the possibility of regulating the processes of nucleation and growth of different polymorphs by careful control of the environmental conditions. One interesting approach is to suppress the growth of a particular crystal form and thereby to promote the growth of the other forms, or at least to present them with a competitive advantage, by addition of "tailor-made" additives or impurities [40]. In this example, certain polypeptides can preferentially induce the crystallization of one of the homochiral crystals of histidine hydrochloride (*R*- or *S*-His·HCl·H_2O) at 25°C instead of the racemic compound (*R*, *S*-His·HCl·$2H_2O$), which is the thermodynamically more stable form below 45°C. In the absence of the additives, the racemic compound crystallizes below 45°C, whereas the homochiral crystals form above 45°C. Other examples of the use of tailor-made additives to direct the crystallization of one crystal form at the expense of another crystal form have been reported, and the number of examples is increasing. In many of these examples the additive preferentially blocks the growth of certain faces of the crystal form that is being suppressed, as in the just-discussed case of histidine hydrochloride [40].

Dunitz and Bernstein [25] pointed out that their examples of disappearing polymorphs involve molecules that can adopt different shapes (i.e., conformational polymorphism). These molecules often possess conformational freedom, or different configurations (epimers, such as α and β sugars), or different arrangements of their parts (e.g., benzocaine picrate) [25]. When present in solution or in the liquid state, the different conformations will exist in a dynamic equilibrium. The most stable conformer in the solution may not necessarily be that present in the thermodynamically most stable crystal form. Dunitz and Bernstein, supporting the scheme presented in Fig. 14 by Etter [22], argue that the rate of formation of nuclei of a stable polymorph could be significantly reduced by a low concentration of the required conformer, while another conformer could be incorporated into the nuclei of a less stable polymorph, which then grows rapidly leading to a metastable crystal [25]. Of course, a polymorph that is metastable at or above ambient temperature might be obtained as the thermodynamically stable form at a lower temperature below the transition point. In preformulation studies of pharmaceutical compounds it is usually, if not always, important to resolve these kinetic and thermodynamic issues. Dunitz and Bernstein [25], echoing Jacewicz and Nayler [30], state that it should always be possible to prepare a previously known polymorph again, although the repreparation will require the appropriate experimental conditions, which might be found quickly or only after some effort. This statement probably expresses the prevailing view and emphasizes the importance of initiating and carrying out a comprehensive screening procedure for polymorphic forms appropriate to the drug substance under consideration [41].

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FT-IR vs. Dispersive Infrared

Theory of Infrared Spectroscopy Instrumentation

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KEYWORDS
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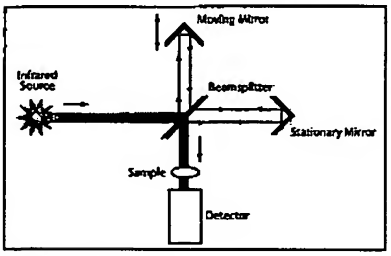
Interferometer
Spectroscopy

The dispersive infrared spectrometer emerged in the 1940's. This design helped to spread the use of infrared spectroscopy as a common analytical technique for organic compound characterization in laboratories. Fourier transform infrared (FT-IR) spectrometers were developed for commercial use in the 1960's, but at that time tended to be used for advanced research only. This was due to the cost of the instrument components and the large computers required to run them. Gradually, technology advancements in computers and instruments have reduced the cost and enhanced the capabilities of an FT-IR. Today, an FT-IR instrument is the standard for organic compound identification work in modern analytical laboratories.

FT-IR: How Does It Work?

An FT-IR instrument uses a system called an interferometer to collect a spectrum. The interferometer consists of a source, beamsplitter, two mirrors, a laser and a detector. The energy goes from the source to the beamsplitter which splits the beam into two parts. One part is transmitted to a moving mirror; one part is reflected to a fixed mirror.

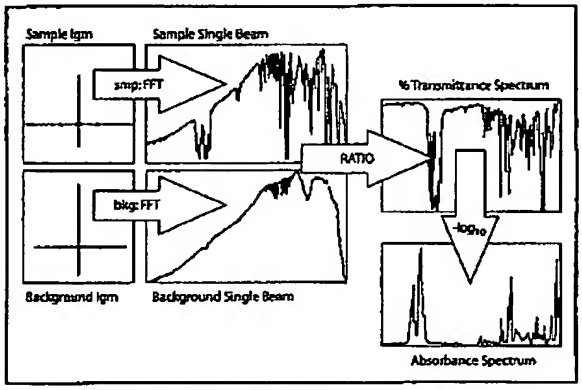


Interferometer Diagram

The moving mirror moves back and forth at a constant velocity. This velocity is timed according to the very precise laser wavelength in the system which also acts as an internal wavelength calibration. The two beams are reflected from the mirrors and recombined at the beamsplitter. The beam from the moving mirror has traveled a different distance than the beam from the fixed mirror. When the beams are combined an interference pattern is created, since some of the wavelengths recombine constructively and some destructively. This interference pattern is called an interferogram. This interferogram then goes from the beamsplitter to the sample, where some energy is absorbed and some is transmitted. The transmitted portion reaches the detector. The detector reads information about every wavelength in the infrared range simultaneously.

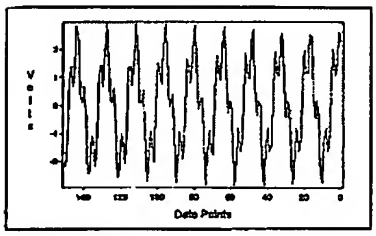
To obtain the infrared spectrum, the detector signal is sent to the computer, and an algorithm called a Fourier transform is performed on the interferogram to convert it into a single beam spectrum. A reference or "background" single beam is also collected without a sample and the sample single beam is ratio-ed to the background single beam to produce a transmittance or "%T" spectrum. This transmittance spectrum can be converted to absorbance by taking the negative $\log_{10}$ of the data points.

The x-axis of the FT-IR spectrum is typically displayed in "wavenumbers", or cm^{-1}. This unit is a product of the Fourier transform algorithm operating on the interferogram and is the reciprocal of the actual wavelength of light measured in centimeters at a point in the infrared spectrum.

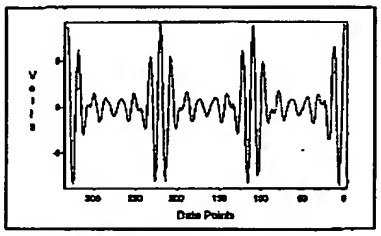


The process of collecting an infrared spectrum in an FT-IR spectrometer

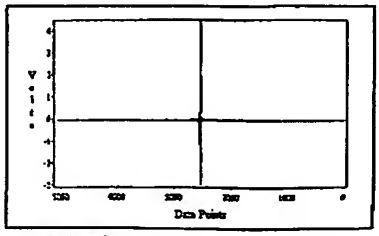
Interference Patterns



Two wavelengths



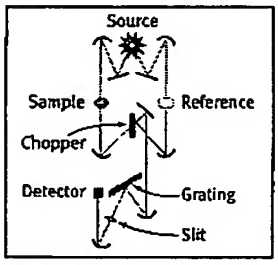
Multiple wavelengths



Infrared interferogram

Dispersive Infrared Instruments

Dispersive infrared instruments are sometimes called grating or scanning spectrometers. A dispersive infrared instrument also has a source and mirrors, but the similarities to an FT-IR end there. The source energy is sent through both a sample and a reference path, through a chopper to moderate the energy reaching the detector, and directed to a diffraction grating. This grating is similar to a prism. It separates the wavelengths of light in the spectral range and directs each wavelength individually through a slit to the detector. Each wavelength is measured one at a time, with the slit monitoring the spectral bandwidth and the grating moving to select the wavelength being measured. The x-axis of a dispersive infrared spectrum is typically nanometers which can be converted to the FT-IR unit wavenumbers by dividing by 10 and taking the reciprocal. An external source of wavelength calibration is required, since there is no high-precision laser wavelength to reference in the system.



Dispersive spectrometer diagram

FT-IR Advantages

There are three major advantages in the performance of an FT-IR spectrometer over a dispersive infrared spectrometer. These advantages have been the reason for the switch to the more modern FT-IR technique in the last decade by infrared spectroscopists.

Multiplex Advantage

An interferometer in an FT-IR instrument does not separate energy into individual frequencies for measurement of the infrared spectrum. Each point in the interferogram contains information from each wavelength of light being measured. Every stroke of the moving mirror in the interferometer equals one scan of the entire infrared spectrum, and individual scans can be combined to give better representation of the actual absorbance of the sample. In contrast, every wavelength across the spectrum must be measured individually in a dispersive spectrometer. This is a slow process, and typically only one measurement scan of the sample is made in a dispersive instrument. The FT-IR advantage is that many scans can be completed and combined on an FT-IR in a shorter time than one scan on a dispersive instrument. The multiplex advantage results in faster data collection of an FT-IR spectrum.

Throughput Advantage

An FT-IR instrument does not use a slit to limit the individual frequency reaching the sample and detector as a dispersive instrument does. There are also fewer mirror surfaces in an FT-IR spectrometer, so there are less reflection losses than in a dispersive spectrometer. Overall, more energy reaches the sample and hence the detector in an FT-IR spectrometer than in a dispersive spectrometer. This means that the signal-to-noise ratio of an infrared spectrum measured on an FT-IR is higher than the signal-to-noise ratio attained on a dispersive instrument. Higher signal-to-noise means that the sensitivity of small peaks will be greater, and details in a sample spectrum will be clearer and more distinguishable in the FT-IR spectrum than the dispersive spectrum of the same sample. In addition, high-resolution measurement of infrared spectra is of higher quality on an FT-IR system. The slit on a dispersive instrument must severely limit the amount of energy reaching the sample in order to measure data points spaced closely together on a high resolution spectrum, resulting in poor quality spectra. The process is also extremely slow due to the coordination of the grating and slit systems to collect the large number of data points required.

Precision Advantage

An FT-IR spectrometer requires the use of a laser to control the velocity of the moving mirror and to time the collection of data points throughout the mirror stroke length for each scan. This laser is also available as a source of wavelength calibration within the instrument. The laser wavelength is a constant value, and the x-axis data points of the FT-IR spectrum are automatically referenced to this known value to maintain internal precision and accuracy of the wavelength positions. Spectra collected with an FT-IR spectrometer can be compared with confidence whether they were collected five minutes or five years apart. This capability is not available on a dispersive infrared system. External calibration standards are required to control the accuracy of a dispersive instrument, making spectra less comparable due to instrumental unknowns during and between scans. Accuracy and precision in infrared spectra are much higher when collected on an FT-IR.

Summary

As discussed here, FT-IR spectrometers are more modern and have numerous performance advantages over dispersive instrumentation. Virtually all infrared spectrometer manufacturers are using FT designs instead of dispersive today. The benefits of upgrading to an FT-IR from an existing dispersive infrared instrument will be immediately evident in spectral quality, data collection speed, reproducibility of data and ease of maintenance and use.

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